been amended to recite that at least one di-tyrosine cross-link is "introduced by genetic engineering". Support for an isolated protein of the invention appears throughout the specification, *inter alia*, at page 55 line 21, page 58 line 12, and page 112 line 28. Support for introduction of a di-tyrosine cross-link by genetic engineering appears throughout the specification, *inter alia*, at page 11 line 24, page 32 line 22, page 33 lines 20-23, page 41 line 33, page 55 line 1, page 57 line 20, page 68 line 16, and page 101 line 20. Claims 21 and 22 are supported in the specification, *inter alia*, at page 10 line 31 to page 11, line 25, page 22 line 14 to page 24 line 29, page 26 line 11 to page 27 line 33, and Example II (page 105 line 26 to page 117 line 22) of the specification.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history prior to examination of this application.

Respectfully submitted,

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Enclosures

EXHIBIT A

Att'y Dkt. No. 9725-005

Application No. 09/837,235 filed April 18, 2001

Marked-Up Version of Claims Amended Herein

April 24, 2002

6. **(Amended)** The method of [claim 6] claim 5, wherein cross-linking is catalyzed by a catalyst selected from the group consisting of polyhistidine, Gly-Gly-His and metalloporphyrin.

9. **(Amended)** [A] An isolated protein cross-linked by the method of claim 1.

10. **(Amended)** [A] An isolated protein comprising at least one di-tyrosine cross-link introduced by genetic engineering, which protein retains at least one function displayed by the protein in the absence of di-tyrosine cross-linking.

19. **(Amended)** The method of claim 18, wherein the cross-link reaction occurs in the presence of an oxidant selected from the group consisting of hydrogen peroxide, oxone, magnesium [monoperxyphthalic] monoperoxyphthalic acid hexahydrate (MMPP), a photogenerated oxidant, and ammonium persulfate.

EXHIBIT B

Att'y Dkt. No. 9725-005

Application No. 09/837,235 filed April 18, 2001

Clean Version of All Pending Claims As Amended Herein

April 24, 2002

1. A method for making a stabilized protein or fragment thereof comprising:
   (a) selecting one or more residue pairs in a polypeptide chain or chains for cross-linking using one or more statistical criteria; and
   (b) cross-linking the residue pairs.

2. The method of claim 1, wherein the stabilized protein or fragment is selected from the group consisting of a hormone, a receptor, a growth factor, an enzyme and an antibody.

3. The method of claim 2, wherein the enzyme is a lipase or the antibody fragment is an Fv fragment.

4. The method of claim 1, wherein the one or more statistical criteria used for selection of residue pairs in step (a) are selected from the group consisting of statistical filter one through statistical filter six.

5. The method of claim 1, wherein tyrosine residues are cross-linked.

6. The method of claim 5, wherein cross-linking is catalyzed by a catalyst selected from the group consisting of polyhistidine, Gly-Gly-His and metalloporphyrin.

7. The method of claim 6, wherein the cross-linked tyrosine residues are introduced into the stabilized protein complex prior to cross-linking by recombinant nucleic acid methods.

8. A method for identifying a residue pair in a polypeptide chain or chains that, following substitution with tyrosine and cross-linking, is least likely to be disruptive of overall protein structure, comprising applying one or more statistical criteria selected from the group consisting of statistical filter one through statistical filter six.

9. An isolated protein cross-linked by the method of claim 1.

10. An isolated protein comprising at least one di-tyrosine cross-link introduced by genetic engineering, which protein retains at least one function displayed by the protein in the absence of di-tyrosine cross-linking.

11. The protein of claim 10, further comprising at least one amino acid which was substituted for a tyrosine residue such that the residue substituted for the tyrosine residue is not cross-linked under cross-linking conditions.

12. The protein of claim 10, wherein the function retained is selected from the group consisting of catalytic activity and binding specificity.

13. The protein of claim 10 which is selected from the group consisting of an enzyme and an antibody or fragment thereof.

14. A pharmaceutical composition comprising the protein of any one of claims 9 to 13.

15. The pharmaceutical composition of claim 14, further comprising a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 14 which is suitable for *in vivo* use in humans.

17. A kit comprising in one or more containers the protein of any one of claims 9 to 13.

18. A method for making a stabilized protein comprising:

(a) selecting one or more residue pairs in a polypeptide chain or chains for cross-linking, wherein the selected residues are tyrosine when cross-linked; and

(b) cross-linking the residue pairs.

19. The method of claim 18, wherein the cross-link reaction occurs in the presence of an oxidant selected from the group consisting of hydrogen peroxide, oxone, magnesium monoperoxyphthalic acid hexahydrate (MMPP), a photogenerated oxidant, and ammonium persulfate.

20. The method of claim 19, wherein cross-linking is catalyzed by a catalyst selected from the group consisting of polyhistidine, Gly-Gly-His and metalloporphyrin.

21. A protein cross-linked by the method of claim 1, wherein the protein is selected from the group consisting of a hormone, a receptor, a growth factor, an enzyme and an antibody.

22. A protein comprising at least one di-tyrosine cross-link, which protein retains at least one function displayed by the protein in the absence of di-tyrosine cross-linking, wherein the protein is selected from the group consisting of a hormone, a receptor, a growth factor, an enzyme and an antibody.